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Metabolic consequences of high mass-transfer hemodialysis

NATHAN TOLCHIN, JIMMY L. ROBERTS, JAMES HAYASHI and EDMUND J. LEWIS

Section of Nephrology, Departments of Medicine and Biochemistry, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois

Metabolic consequences of high mass-transfer hemodialysis. The metabolic fate of acetate (Ac) infused during hemodialysis and the acid-base changes attendant to its conversion to bicarbonate were studied in 20 patients. Twenty-eight studies were performed under three conditions: group 1, 40 mmoles/liter of Ac dialysate; group 2, 30 mmoles/liter of Ac dialysate; and group 3, bicarbonate-buffered dialysate. Fasting patients were dialyzed using 2.5 m² hollow fiber dialyzers. Patients remained fasting for 4 hr after dialysis and were observed for 48 hr. Total acetate infused was highest for group 1 patients. The maximum acetate utilization rate was 48 μmoles/min/kg of body wt. Peak plasma acetate values were 5.1 mmoles/liter when the rate of acetate infusion approximated maximum utilization, and were 10.2 mmoles/liter when the maximum utilization rate was exceeded. Significant bicarbonate removal occurred during hemodialysis (group 1, 848 mmoles; group 2, 676 mmoles). In group 1 and 2 patients, the intradialytic bicarbonate removal rate exceeded the bicarbonate generation rate, causing serum bicarbonate concentrations to decrease, and peak postdialysis bicarbonate concentrations did not occur until four hours. The carbon dioxide pressures of groups 1 and 2 dropped significantly early in dialysis and accounted for any pH rise occurring during dialysis. The proportion of estimated acetate metabolized to bicarbonate was 93.5% in group 1 and 91.1% in group 2. Acute changes in plasma lipid patterns were the same in all groups. These results indicate that high mass-transfer hemodialysis can result in excessive acetate infusion, marked bicarbonate removal, and carbon dioxide dialysance, which have significant impact on the patient's acid-base status, and that immediate equimolar conversion of acetate to bicarbonate does not occur during dialysis.

Conséquences métaboliques de l'hémodialyse à haut rendement de transfert de solutés. Le devenir métabolique de l'acétate (Ac) administré au cours de l'hémodialyse et les modifications acido-basiques consécutives à sa conversion en bicarbonate ont été étudiés chez 20 malades. Ving-huit études ont été réalisées dans 3 conditions: groupe 1, dialysat 40 mM en Ac; groupe 2, dialysat 30 mM en AC; et groupe 3: dialysat tamponné avec bicarbonate. Les malades à jeun ont été dialysés au moyen de fibres creuses de 2,5 m². Les malades sont restés à jeun pendant 4 hr après la dialyse et ont été suivis pendant 48 hr. La quantité totale d'Ac transférée a été la plus élevée chez les malades du groupe 1. Le débit maximum d'utilisation de l'acétate a été de 48 μmoles/min/kg. La valeur la plus élevée de l'acétate plasmatique a été de 5,1 mmoles/liter quand le débit de transfert était voisin de l'utilisation maximale et de 10,2 mmoles/liter quand l'utilisation maximale a été dépassée. Une soustraction significative de bicarbonate a été observée au cours de l'hémodialyse (groupe 1, 848 mmoles; groupe 2, 676 mmoles). Dans les groupes 1 et 2 la soustraction de bicarbonate intradialytique a été supérieure à la génération de bicarbonate ce qui a déterminé une baisse de bicarbonate pendant dialyses. La valeur maximale de bicarbonate post-dialytique n'a pas été obtenue avant la 4e heure. Les P_{CO_2} des groupes 1 et 2 ont baissé significativement au début de la dialyse et les valeurs expliquaien l'augmentation du pH observée pendant la dialyse. La proportion d'acétate métabolisée en bicarbonate a été de 93.5% dans le groupe 1 et de 91,1% dans le groupe 2. Les modifications aiguës des lipides du plasma ont été semblables dans les différents groupes. Ces résultats indiquent que l'hemodialyse à haut rendement de transfert peut avoir pour conséquence une administration excessive d'acétate, une soustraction de bicarbonate importante et une dialysance du gaz carbonique qui ont des conséquences importantes sur l'état acido-basique du malade. Ils indiquent aussi que la conversion équimolaire de l'acétate en bicarbonate ne se produit pas immédiatement au cours de la dialyse.

The correction of the metabolic acidosis of uremia is a fundamental function of hemodialysis. The alkalinizing salt in almost universal use in dialysate is sodium acetate. Its choice to replace sodium bicarbonate presumes a rapid peripheral utilization and equimolar oxidative generation to sodium bicarbonate via the tricarboxylic acid pathway [1]. It has been estimated that man can metabolize up to 300 mmoles/hr of acetate [2], but recent evidence suggests that the maximum rate of utilization in dialysis patients is somewhat slower [3]. Kveim estimated the maximum utilization rate to be 3.5 mmoles/hr/kg of body wt [3].

In recent years, the use of large surface area dialyzers, higher blood flows, and high dialysate acetate concentrations (35 to 40 mmoles/liter) has resulted in the administration of a considerable acetate load to hemodialysis patients. Some authors [4, 5] have implied that contemporary hemodialysis methods may cause acetate infusion at a rate above the maximum at which it can be metabolized via the tricarboxylic acid cycle. A possible consequence of a massive acetate load is diversion of the acetate into alternate metabolic pathways. Acetate occupies a central role in carbohydrate and lipid metabolism. After cellular conversion of acetylcoenzyme A, it can be metabolized to carbon dioxide and water; it can undergo condensation to malonylcoenzyme A and enter fatty acid synthesis, or it can be converted to hydroxy-

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methylglutarylcoenzyme A and enter metabolic pathways forming ketone bodies, terpenes, and cholesterol [6, 7].

We have investigated hemodialysis patients to determine: *1)* the acetate metabolic rate under circumstances of hemodialysis; *2)* the effects of rapid administration of large amounts of sodium acetate on acute alterations of acid-base status; *3)* the proportion of acetate entering the tricarboxylic cycle and that which may be available for entry into alternate metabolic pathways; and *4)* the presence of possible acute alterations of plasma lipid patterns which could be attributable to the integral role of acetylcoenzyme A in lipid metabolism.

Methods

Patients. Outpatients with a mean age of 47.1 ± 9.7 (± 1SD) yr, who had chronic renal failure with an endogenous creatinine clearance of less than 3 ml/min and a residual urine volume of 200 to 800 ml/day, were chosen for study. All patients were receiving 6-hr hemodialyses three times a week, using either 1.0 m^2 coil or 1.3 m^2 hollow fiber dialyzers. Patients receiving this treatment for at least three consecutive months were considered to be "established" on the therapy. "New" patients had received treatment for less than one month. Individuals with diabetes mellitus, hepatic insufficiency, pericarditis, congestive heart failure, or a hematocrit less than 20% were excluded. One patient had an abnormal hemoglobin (30% Hgb S).

Each patient was on a diet consisting of at least 0.75 g of protein/kg of body wt per day with carbohydrate and polyunsaturated fat individually prescribed to maintain an ideal body weight. Drug therapy included multivitamins, folate, aluminum hydroxide, and ferrous fumarate. In addition, some patients received antihypertensives (6 of 20 patients) or adrogenic steroids (2 of 20 patients) at the time of study.

Twenty-eight studies were performed on 20 patients under conditions of *a)* high dialysate acetate concentration (group 1), *b)* moderate dialysate acetate concentration (group 2), and *c)* buffered bicarbonate dialysate with no acetate (group 3) (Table 2). Six patients were studied twice, one person was studied three times.

Hemodialysis procedure and performance. Glucose-free dialysate was used exclusively in this study. The dialysate of patients in group 1 was continuously prepared from a commercial concentrate (Hemotrate®, McGaw, Glendale, CA) and delivered by a single pass proportioning unit (Milton Roy, Park Ridge, IL) at a rate (Q_D) of 500 ml/min (volumetric calibration), yielding a mean acetate concentration of 40 mmoles/liter at the dialyzer inlet (Table 1). The dialysate of patients in group 2 was batch-prepared from concentrate (Hemotrate®) in 200-liter volumes in a recirculating single pass system (Travenol, Morton Grove, IL) and delivered to the recirculating chamber at a Q_D of 500 ml/min. A negative pressure converter (Cordis Dow, Miami, FL) delivered dialysate with a mean dialyzer inlet acetate concentration of 30 mmoles/liter.

The dialysate of patients in group 3 was batch-prepared by adding the following salts to each 200-liter bath: sodium chloride, 1150 g; sodium bicarbonate, 604 g; potassium chloride, 30 g; magnesium chloride, 30 g; and calcium chloride, 32 g. Initially, the pH was adjusted to 7.4 with 6 N hydrochloric acid and maintained by bubbling 10% carbon dioxide and balanced air mixture through the reservoir and recirculating chambers at 5 to 7 liters/min. The group 3 delivery system was the same as in group 2 studies. Electrolyte and acetate dialysate concentrations were sampled from the dialyzer inlet. All patients were dialyzed with 2.5 m^2 hollow fiber artificial kidneys (Cordis Dow, Miami, FL).

Vascular access was provided by external shunts (5 patients), a bovine heterograft (1 patient), and arteriovenous fistulae (14 patients). In the fistula group, a separate true arterial line was established at a distant site. A double roller blood pump (Travenol, Morton Grove, IL) was used; blood flow rates (Q_B) were calibrated volumetrically *in vitro* and verified during dialysis with a 50-cm race track and blood flow monitor (Renal Systems, Minneapolis, MN). Alterations in body weight were minimized by keeping blood flow rates and dialysate negative pressure (50 mm Hg) constant throughout dialysis. Ultrafiltration rate (Q_F) in group 1 patients was estimated from careful measurements of fluid balance and weights; for groups 2 and 3, Q_F was determined from the difference of recirculating chamber inlet and outlet dialysate volumes collected over 5-min periods. Ultrafiltrate and blood loss from samples were replaced with normal saline. Anticoagulation was achieved with bolus doses of heparin given as 60 U/kg of body wt initially, 15 U/kg at hours one and two, and 7.5 U/kg at hour three.

Fasting (12 hr) patients received a 4-hr hemodialysis and remained fasting after dialysis for 4 hr. Weight was taken before and after dialysis. For those individuals with significant urine production, the bladder was emptied prior to dialysis, and urine was collected for renal acetate clearance and bicarbonate excretion. Follow-up specimens were drawn from fasting patients (12 hr) at 24 and 48 hr after initiation of hemodialysis.

Blood and dialysate samples for electrolytes, urea,

Table 1. Measured dialysate solute characteristics

Solute	Group 1 *mEq/liter*[a]	Group 2 *mEq/liter*[a]	Group 3 *mEq/liter*[a]
Sodium	139.0 ± 1.0	136.0 ± 3.5	132.0 ± 4.0
Acetate	40.0 ± 1.8	30.0 ± 2.7	0.0
Bicarbonate	0.0	4.2 ± 1.3	30.2 ± 2.8
Chloride	108.0 ± 3.0	104.0 ± 2.3	103.0 ± 4.0
Potassium	2.0 ± 0.1	2.1 ± 0.2	2.0 ± 0.2
Calcium	3.3 ± 0.5	3.2 ± 0.4	3.1 ± 0.4
Magnesium	1.6 ± 0.2	1.4 ± 0.3	1.6 ± 0.3

[a] ± 1SD.

creatinine, uric acid, and glucose were drawn hourly with the exception of glucose and uric acid (2nd and 4th hr only) and were measured by standard techniques (Technicon). The clearance (Table 3) and dialysance for urea, creatinine, bicarbonate, uric acid, and glucose for each of the study groups was determined from plasma samples drawn simultaneously across the dialyzer; no attempt was made to correct for solute disequilibrium which might exist between plasma and red blood cells. Calculations for clearance and dialysance were based on a modification of Wolf's formulae [8] (Appendix, equations 1a and b).

Blood samples for blood gas analysis (Table 4), electrolytes, lactate, and pyruvate (Table 6) were drawn before, during, and after dialysis. Samples for acetate determinations were drawn hourly during dialysis (Fig. 1), serially immediately after dialysis (Fig. 2), and monitored subsequently at 8, 24, and 48 hr after initiation of the study. Specimens for total cholesterol, fatty acids, triglycerides, lipoprotein electrophoresis, acetoacetate, acetone, ethanol, and acetaldehyde were collected sequentially throughout the study (Figs. 3 and 4). True arterial samples for acetate and gas analysis were obtained in fistula patients, along with the simultaneous arterial dialyzer line specimens.

Acid-base metabolism. Blood samples for pH, carbon dioxide pressure (pCO_2), and oxygen pressure (pO_2) were drawn anaerobically in heparinized syringes, iced, and analyzed immediately with gas analyzers (Radiometer, Copenhagen, Denmark; Instrumentation Laboratory, Lexington MA). These instruments were calibrated prior to each use, and accuracy was verified using standards (Blood Gas Analyzer Systems Control®, General Diagnostics, Morris Plains, NJ) over a pH range of 7.03 to 7.63; the pH determinations varied ± 0.02 pH units. The variance of the pCO_2 (± 1.3 mm Hg) and the pO_2 (± 9.1 mm Hg) was determined under the same pH conditions. Dialysate samples were processed similarly. Minute ventilation volume (MVV) was measured with a respirometer (Wright).

Table 2. Patient groups

Variable[a]	Group 1 40 mmoles acetate	Group 2 30 mmoles acetate	Group 3 Bicarbonate bath
N (studies)	8	10	10
Age, *years* ± SD	46.5 ± 9.0	43.1 ± 15.0	49.0 ± 11.0
Established patients, %	50%	60%	60%
Male patients, %	63%	40%	60%
Prior interdialytic interval, *hr* ± SD	50.0 ± 12.0	48.5 ± 20.0	44.0 ± 14.0
Predialysis serum creatinine *mg/dl/kg* ± SD	0.14 ± 0.04	0.15 ± 0.03	0.14 ± 0.03

[a] No statistical difference among groups for each variable.

Table 3. *In vivo* performance characteristics of the 2.5 m^2 hollow fiber artificial kidney

Solute	Clearance ml/min ± SEM Group 1 (*N* = 8)	Group 2 (*N* = 10)	Group 3 (*N* = 10)
Creatinine	169.0 ± 6.3	135.4 ± 6.6[c]	138.3 ± 5.7[b]
Urea	220.0 ± 6.0	122.7 ± 2.2[c]	124.7 ± 4.5[b]
Bicarbonate	208.0 ± 9.2	130.2 ± 7.1[c]	—
Uric acid	147.0 ± 5.2	—	107.4 ± 4.7[b]
Glucose	175.8 ± 10.9	—	124.2 ± 3.2[b]
Q_B[a]	280.0 ± 10.0	270.2 ± 10.0	291.0 ± 4.2

[a] No statistical significance between groups for blood flow (Q_B).
[b] Significance group 1 vs. 3 ($P < 0.001$).
[c] Significance group 1 vs. 2 ($P < 0.001$).

Actual bicarbonate was calculated by the methods of Sigaard-Anderson [9] and Thomas [10]. The anion gap was determined as follows: (sodium + potassium) − (chloride + bicarbonate). Lactate was measured using the Dupont ACA enzymatic (NAD-LDH) system. Pyruvate was determined by previously reported techniques [11].

Acetate metabolism. For group 1 and 2 patients, plasma acetate concentrations were determined for calculation of acetate kinetics. Because of disequilibrium between red blood cell (RBC) and plasma acetate concentrations, separate studies were undertaken to determine arterial and venous dialyzer RBC and plasma acetate concentrations under the same conditions as those of the study groups. Twenty studies were performed in four patients at regular intervals during a four-hour dialysis period. Heparinized blood was iced immediately, and duplicate samples were *1)* sonicated and frozen immediately for subsequent whole blood acetate determination, or *2)* centrifuged, the plasma removed, RBCs sonicated, and the separate plasma and RBC aliquots frozen immediately for subsequent plasma and RBC acetate determinations. The hematocrit and volume of RBC ghosts of sonicated whole blood were determined for each sample. Red blood cell ghosts accounted for less than 1% of whole blood volume.

Total blood acetate concentration measured from

Table 4. Respiratory and metabolic changes during and after hemodialysis

Hr	pH, ± SD			P_{CO_2}, *mm Hg*			HCO_3, *mmoles/liter*		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
0	7.38 ± 0.04	7.41 ± 0.02[a]	7.38 ± 0.04	35.4 ± 4.1	35.5 ± 2.6	35.6 ± 4.2	20.5 ± 3.9	21.7 ± 2.4	19.7 ± 1.9
1	7.38 ± 0.06	7.42 ± 0.04	7.40 ± 0.03	28.8 ± 4.2	29.3 ± 4.3[a]	34.9 ± 4.3[b]	16.2 ± 2.1[c]	18.3 ± 1.8[a]	20.9 ± 2.2[d]
2	7.42 ± 0.05	7.43 ± 0.04	7.42 ± 0.03	25.6 ± 4.2	28.0 ± 3.4[e]	34.5 ± 4.3[d]	15.4 ± 2.1[c]	18.5 ± 2.4[f]	21.4 ± 1.7[d]
3	7.41 ± 0.04	7.43 ± 0.04	7.43 ± 0.03	25.8 ± 4.0	28.4 ± 5.1[e]	34.7 ± 4.0[d]	15.8 ± 2.3[g]	18.5 ± 2.6[f]	22.3 ± 2.2[d]
4	7.41 ± 0.04	7.45 ± 0.04	7.45 ± 0.02	25.2 ± 4.2	27.9 ± 4.3[f]	33.2 ± 5.1[h]	15.6 ± 2.1[g]	19.2 ± 3.1[a]	22.6 ± 2.1[d]
8	7.48 ± 0.05	7.47 ± 0.05	7.44 ± 0.03	33.7 ± 4.5	32.0 ± 3.1	32.9 ± 2.5	23.8 ± 2.4	22.7 ± 3.0	21.6 ± 1.4
24	7.42 ± 0.04	7.41 ± 0.04	7.41 ± 0.03	34.7 ± 2.9	34.9 ± 2.0	35.0 ± 3.1	22.3 ± 2.2	21.9 ± 2.8	20.5 ± 1.8
48	7.39 ± 0.04	7.40 ± 0.03	7.37 ± 0.04	34.1 ± 2.6	34.8 ± 3.9	33.0 ± 2.8	19.5 ± 1.9	20.9 ± 2.2[a]	18.5 ± 1.7

[a] Significance, group 2 vs. 3 ($P < 0.05$).
[b] Significance, group 1 vs. 3 ($P < 0.05$).
[c] Significance, group 1 vs. 2 ($P < 0.01$).
[d] Significance, group 1 vs. 3 ($P < 0.001$).
[e] Significance, group 2 vs. 3 ($P < 0.005$).
[f] Significance, group 2 vs. 3 ($P < 0.01$).
[g] Significance, group 1 vs. 2 ($P < 0.05$).
[h] Significance, group 1 vs. 3 ($P < 0.01$).

sonicated whole blood and total blood acetate calculated from the plasma and RBC acetate concentrations were within ± 1%. There were no significant differences in the arterial RBC to plasma acetate ratios at one, two, and four hours of dialysis ($P > 0.1$). This was also true for the venous dialyzer outlet values. Arterial RBC acetate was 0.59 ± 0.09 (± 1 SD) that of arterial plasma acetate concentration, and venous dialyzer line RBC acetate was 0.49 ± 0.08 that of the venous line plasma acetate (Appendix, equation 2b and c).

Samples for group 1 and 2 studies were iced, separated, and analyzed immediately, or frozen and stored. There was no loss of acetate in frozen samples stored for as long as three weeks.

For acetate analysis, samples (plasma, sonicated RBCs or whole blood, and dialysate) were diluted with distilled water, acidified with hydrochloric acid, and analyzed in a gas chromatographic apparatus. The analysis conditions were: Porapak Q column (91 × 0.2 cm) in glass; temperature, 160°C; nitrogen flow rate, 40 ml/min; and detection with a flame ionization detector. Acetate concentration was calculated by comparing the peak height of the patients' chro-

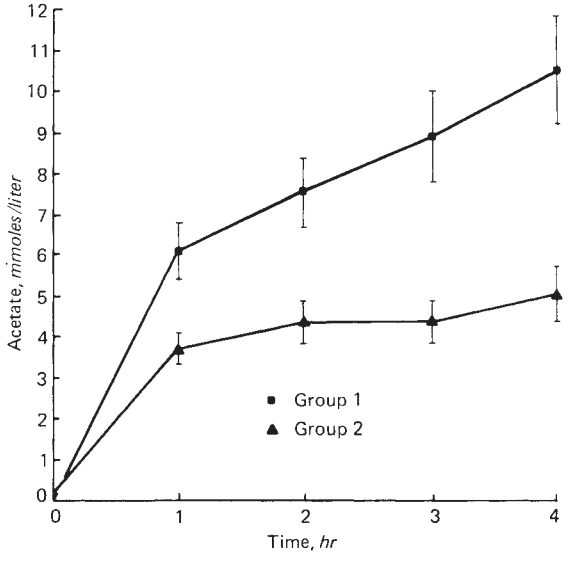

Fig. 1. *Plasma acetate concentrations during hemodialysis.* ✚ represents ± SEM.

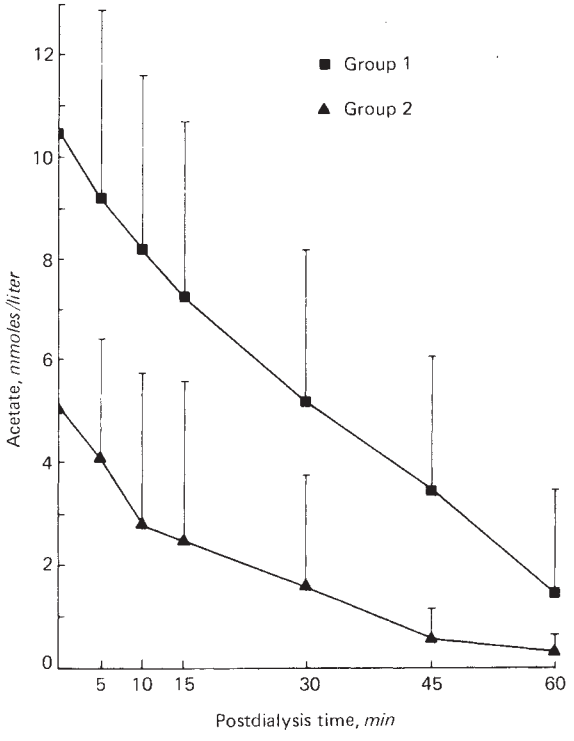

Fig. 2. *Disappearance of plasma acetate in the immediate postdialysis period.* ↓ represents 1 SD.

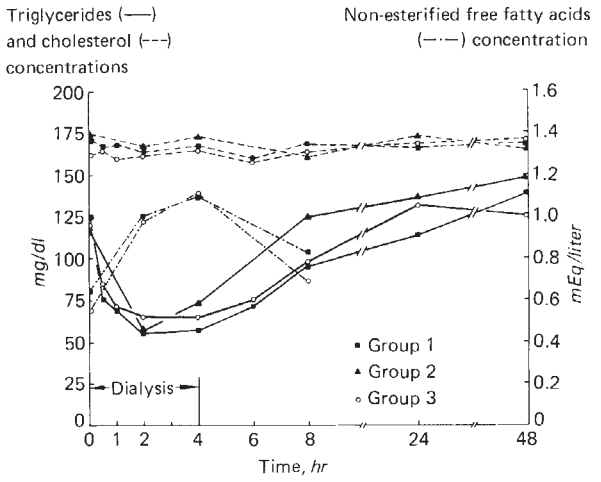

Fig. 3. *Plasma lipid changes during and after dialysis.*

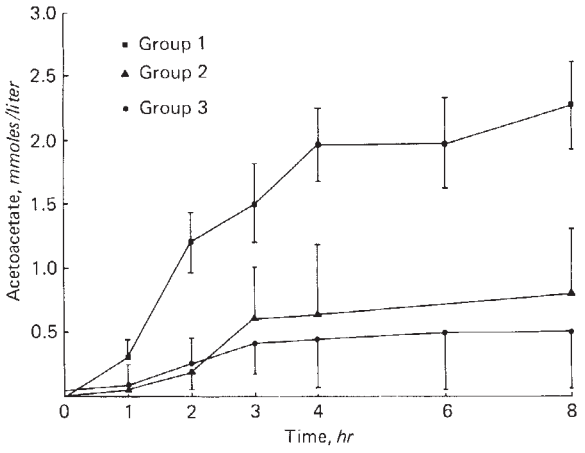

Fig. 4. *Serum acetoacetate concentration during and after dialysis.* | represents 1 SD. Group 1 levels were significantly greater than Group 2 or 3 levels by mid-dialysis ($P < 0.005$).

matogram to four simultaneously run acetic acid standards ranging from 20 to 80 mg/dl (undiluted). The standard solutions were calibrated prior to each group of determinations. Peak chromatographic height showed a linear relation to increasing concentrations of the standard solutions. The coefficient of variance for this method is ±3.1% over a range of plasma acetate concentrations of 0.1 mmoles/liter, to 240 mmoles/liter. Values less than 0.1 mmoles/liter were reported as trace amounts. With this method, 20 normal fasted volunteers had no detectable circulating acetate. Trace amounts of circulating acetate were detected in only 2 out of 84 measurements in fasting dialysis patients.

Mass transfer of acetate (acetate infused) was calculated (Appendix, equation 3) for each hour of dialysis from the mass transfer rate for acetate (Appendix, equation 2a). The average rate of acetate infusion during dialysis was calculated from the total acetate infused (Appendix, equation 4). The maximum rate of utilization of exogenous acetate was calculated from hourly true arterial levels when consecutive values remained constant or increased slightly (<10%). Assuming this represented stabilization of the total body acetate pool, the amount metabolized in that hour was considered equivalent to the amount infused (Appendix, equation 5) [3]. Acetate disappearance rate was calculated from the postdialysis data (Appendix, equation 6).

Estimation of entry of sodium acetate into the tricarboxylic acid cycle. The determination of the proportion of infused acetate metabolized in the tricarboxylic acid cycle was carried out by estimation of changes in the total body bicarbonate during and after acetate infusion (Table 5).

The total amount of acetate infused during hemodialysis was calculated using the Fick principle (Appendix, equations 3a and b). At the start of dialysis, the total body bicarbonate was estimated from the actual serum bicarbonate concentration (Appendix, equation 7a). The bicarbonate space was taken to be 60% of the total body wt [12–14]. The rate and total amount of bicarbonate removed during hemodialysis were estimated (Appendix, equations 7b and c, 10). Total bicarbonate generated was calculated for the period during and after dialysis (Appendix, equations 7d, e, and f). The peak postdialysis serum bicarbonate concentration was used to compute the postdialysis total body bicarbonate concentration and the total bicarbonate generated (Appendix, equation 7e

Table 5. Estimated acetate and bicarbonate kinetics during hemodialysis[a]

Groups	Total bicarbonate removed (T. HCO_{3_R}) *mmoles* ± SD	Total bicarbonate generated (T. HCO_{3G}) *mmoles* ± SD	Total infused acetate (T. Inf. Ac) *mmoles* ± SD	Acetate converted (M_{Ac}) % ± SEM
1	848.0 ± 100.0[b]	980.6 ± 214.0[b]	1048.3 ± 100.5[b]	93.5 ± 4.8
(range)	(701.0 to 103.0 mmoles)	(632.0 to 1193.0 mmoles)	(966.0 to 1190.0 mmoles)	(66.0 to 106.0%)
2	676.0 ± 154.0	723.9 ± 190.0	780.4 ± 145.6	91.1 ± 3.5
(range)	(400.0 to 883.8 mmoles)	(467.0 to 960.0 mmoles)	(568.0 to 959.0 mmoles)	(77.0 to 106.0%)

[a] The method for calculating the kinetic data is outlined in the Appendix (equations 7a-f, 8).
[b] Significance 1 vs. 2, $P < 0.01$.

and f). The proportion of infused acetate entering the tricarboxylic acid cycle was estimated from the apparent bicarbonate generation (Appendix, equation 8). The calculation of the rate of bicarbonate generation during dialysis was based on changes in total body bicarbonate estimates (Appendix, equations 9a, b, and c).

Lipids and acetate metabolites. Total serum cholesterol was measured by autoanalyzer using the Zak-Slatkis color reaction after isopropanol extraction (Technicon). Total triglycerides were also measured by autoanalyzer using phospholipid extraction, saponification of the triglycerides, and release and measurement of the freed glycerol [15]. Lipoprotein electrophoresis was performed with agarose gel (Corning ACI, Universal Electrophoresis System). Serum acetone was measured by gas chromatography [16]. Acetoacetate was measured using serial sample dilutions [17]; the trace amount of acetoacetate was the dilutional endpoint of the assay. Comparison acetoacetate standard solutions were used to determine the concentration in the patients' samples (Fig. 4). Increasing concentrations of the standard solutions demonstrated a linear relationship to the detectability of acetoacetate in progressively more dilute samples. Acetoacetate presence in an undiluted sample represented a concentration of 0.5 mmoles/liter, a positive 1:2 dilution represented 1.0 mmoles/liter, a 1:4 dilution was equivalent to 1.7 mmoles/liter, and a 1:8 dilution equaled 3.0 mmoles/liter. The coefficient of variance of this method was ±8.0%; the recovery rate of the method was 99.0%. Gas chromatography was used to measure ethanol and acetaldehyde. Analysis conditions were similar to those of acetate determinations, except for lower column temperatures.

Plasma samples for total nonesterified fatty acids were iced, immediately separated, and frozen at −70°C. These were analyzed according to published techniques [18,19]. Results were reported in mEq/liter to avoid assumption of fatty acid chain length.

Statistical analysis. Group means were examined for significant differences by Student's *t* test. Correlation of two variables was done by linear regression analysis [20].

Results

Patients. Patients in all study groups tolerated hemodialysis without obvious clinical adverse effects. No significant episodes of hypotension (systolic blood pressure < 110 mm Hg) occurred during dialysis. The body weight decrease in group 1 was 0.5 kg ± 0.2 (± 1 SD), in group 2 it was 0.7 ± 0.2 kg, and in group 3, 0.6 ± 0.1 kg; there were no significant weight differences among groups or between pre- and postdialysis weights ($P > 0.1$). The mean serum creatinine values at 48 hr were not significantly different ($P > 0.1$) from the predialysis values (Table 2).

Solute mass-transfer. The 2.5 m² hollow fiber artificial kidney provided efficient solute transfer during hemodialysis (Table 3). The clearance of small solutes was significantly greater for group 1 studies than group 2 and 3 studies. In group 2 and 3 patients, however, mean dialysance values for the same solutes were not significantly different from group 1 (group 1: creatinine, 169.0 ml/min ± 6.3 [± 1 SEM]; urea, 220.6 ± 6.0 ml/min; group 2: creatinine, 171.9 ± 4.0 ml/min; urea, 210.1 ± 8.4 ml/min; group 3: creatinine, 173.0 ± 5.3 ml/min; urea, 221.0 ± 8.7 ml/min) ($P > 0.1$), verifying that dialyzer performance was consistent throughout the investigation. Mean blood flow values were similar in all groups. During hemodialysis, glucose transfer resulted in the loss of 180.0 ± 3.0 mmoles (± 1 SD) of glucose from each patient. A small concentration of glucose (27.0 ± 1.4 mg/dl) accumulated in the recirculating chamber during group 2 and 3 studies.

Acid-base metabolism. Several significant metabolic and respiratory changes occurred in the patients in groups 1 and 2 hemodialyzed with acetate-containing dialysate (Table 4). The arterial carbon dioxide pressure (P_{CO_2}) dropped during dialysis in group 1 and 2 patients; this was associated with low blood P_{CO_2} measurements (10 mm Hg or less) in the venous dialyzer line. Upon completion of dialysis, the arterial P_{CO_2} rose rapidly. Group 3 patients had no depression of arterial P_{CO_2} and significantly ($P > 0.005$) higher dialyzer venous blood values (38.2 ± 0.7 mm Hg). In groups 1 and 2, arterial P_{O_2} decreased by 10% early in dialysis and then returned to baseline values; P_{O_2} changes for group 3 patients were not significant. There was a small decrease in the minute ventilation volume at one hour, but the values during or after dialysis were not significantly different from the predialysis values of 7.5 liters/min ± 2.1 (± 1 SD) (group 1), 9.5 ± 3.0 liters/min (group 2), and 7.4 ± 3.0 liters/min (group 3).

In groups 1 and 2, serum bicarbonate decreased during dialysis (Table 4). The mean rate of bicarbonate removal ($\dot{R}HCO_3$) was 47.5 μmoles/min/kg of body wt ± 7.1 (± 1 SD) in group 1 and 44.9 ± 13.4 μmoles/min/kg in group 2. The calculated intradialytic rate of bicarbonate generation ($\dot{R}HCO_3$) was 42.9 ± 11.0μmoles/min/kg in group 1 and 41.9 ± 13.0 μmoles/min/kg in group 2. Hence, the rate of bicarbonate removal appeared to exceed that of generation in both groups, and no intradialytic progress was made in correcting the predialysis total body

bicarbonate deficit. In group 3 patients, the net influx of bicarbonate across the dialyzer into blood resulted in a prompt increase of serum bicarbonate.

In group 2, the bicarbonate concentration of the recirculating chamber dialysate equilibrated at 4.2 ± 1.3 mmoles/liter by mid-dialysis. This is in contrast to the predictable absence of bicarbonate in the inlet dialysate of the single pass system used in the group 1 patients. As a result of the lower concentration gradient, less total bicarbonate was removed from group 2 patients (676.0 ± 154.0 mmoles) than from group 1 patients (848.0 ± 100 mmoles) (Table 5).

After cessation of dialysis, bicarbonate continued to be generated from the remaining total body acetate pool. Serum bicarbonate concentrations increased until maximum levels were attained at four hours after dialysis in groups 1 and 2 (Table 4). This rise was significantly greater ($P < 0.01$) for group 1 than for group 2 patients. At six hours after dialysis (two patients from each group) no further bicarbonate increase from four hour postdialysis levels had occurred. There followed a steady decline to predialysis values. As would be expected, there was no postdialysis rise in the arterial bicarbonate concentration in group 3 patients.

The initial acid-base status of the patients studied was consistent. Twenty-three of twenty-eight predialysis blood gas values indicated complete respiratory compensation for the underlying metabolic acidosis (pH > 7.35). In the remaining five individuals, the mean predialysis pH was 7.33 ± 0.01. Four of the five were "new" patients to the program, but none had an excessive preceeding interdialytic interval (46.0 ± 2.8 hr). Acid-base metabolism was otherwise similar in both "new" and "established" patients.

Hemodialysis resulted in higher blood pH values for all groups (Table 4). In group 1, the rise, compared to predialysis values, does not attain statistical significance until four hours after dialysis ($P < 0.05$); the increase in group 2 was never statistically significant. At the conclusion of dialysis, none of the patients in group 1 and 2 had corrected their diminished total body bicarbonate.

The anion gap increased in group 1 and 2 patients in association with increased plasma acetate levels (Table 6). No significant changes in lactate or pyruvate occurred. The anion gap narrowed significantly immediately after dialysis, concomitant with the decrease in circulating acetate.

Acetate metabolism. The mean acetate infusion rate ($\bar{N}_{Ac}$) for group 1 (59.8 μmoles/min/kg of body wt ± 10.0 [± 1 SD]) was significantly greater than for group 2 patients (49.7 ± 8.0 μmoles/min/kg) ($P < 0.01$). With the onset of dialysis, there was a prompt increase in true arterial plasma acetate values (Fig. 1). In group 2, these tended to plateau by mid-dialysis. The values in group 1 were significantly greater than in group 2 at all times and rose continuously throughout dialysis ($P < 0.01$). The apparent maximum rate of utilization of exogenous acetate was calculated to be 48.0 ± 9.0 μmoles/min/kg (± 1 SD).

Circulating acetate disappeared at a constant rate for the first ten minutes after the cessation of dialysis (Fig. 2); the k_{Ac} was 200 ± 50 μmoles/liter/min (± 1 SD) in group 1 and 184 ± 50 μmoles/liter/min in group 2 ($P > 0.1$). In group 2, small (<1 mmole) amounts of acetate were found at one hour after dialysis in only two patients. In contrast, four group 1 patients had circulating levels of 1.0 to 5.1 mmoles/liter at the same time. Three of these four patients were "new" patients. No circulating acetate was found four hours after dialysis in any patient. No other differences in acetate metabolism were noted between "new" and "established" patients.

Estimation of entry of acetate into tricarboxylic acid cycle. The amount of acetate infused during dialysis was a direct function of the dialysate acetate concentration (Table 5). The mean total amount of acetate infused was 1048.3 μmoles ± 100.5 mmoles (±1 SD) in

Table 6. Anion gap, lactate and pyruvate changes during and after hemodialysis

Hr	Anion gap, *mEq/liter* ± SD			Lactate, *mmoles/liter*			Pyruvate, *mmoles/liter*		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
0	22.4 ± 3.8	20.2 ± 3.6	21.4 ± 3.1	0.98 ± 0.3	0.93 ± 0.4	0.04 ± 0.1	0.08 ± 0.01	0.08 ± 0.05	0.05 ± 0.02
1	28.1 ± 2.5[a]	23.1 ± 4.3[b]	18.8 ± 3.0[c]						
2	28.2 ± 2.4	24.7 ± 5.2[b]	18.7 ± 2.6[c]	1.10 ± 0.2	0.86 ± 0.4	0.86 ± 0.1	0.08 ± 0.01	0.08 ± 0.04	0.05 ± 0.02
3	29.3 ± 2.8[a]	23.7 ± 4.5[b]	17.2 ± 2.0[c]						
4	28.9 ± 3.0	24.6 ± 6.0[b]	17.9 ± 2.2[c]	0.86 ± 0.3	0.94 ± 0.3	0.80 ± 0.3	0.04 ± 0.02	0.09 ± 0.03	0.06 ± 0.02
8	18.6 ± 3.1	20.1 ± 5.1	20.4 ± 2.3	0.95 ± 0.4	0.94 ± 0.4	0.76 ± 0.3	0.04 ± 0.02	0.11 ± 0.03	0.06 ± 0.03
24	21.7 ± 3.1	21.4 ± 3.0	20.5 ± 3.3	1.13 ± 0.4	1.10 ± 0.5	0.94 ± 0.4	0.07 ± 0.04	0.12 ± 0.04	0.04 ± 0.02
48	22.5 ± 2.1	21.9 ± 3.3	22.6 ± 3.1	1.00 ± 0.4	0.91 ± 0.4	0.84 ± 0.2	0.04 ± 0.02	0.09 ± 0.05	0.04 ± 0.02

[a] Significance, group 1 vs. 2 ($P < 0.05$).
[b] Significance, group 2 vs. 3 ($P < 0.01$).
[c] Significance, group 1 vs. 3 ($P < 0.01$).

group 1; this was significantly greater than that infusion into group 2 (780.4 ± 145.6) ($P < 0.01$). The greater acetate infusion for group 1 ultimately resulted in a larger amount of bicarbonate generated over the eight-hour period comprising dialysis and the first four hours after dialysis (group 1, 980.6 ± 214.0 mmoles; group 2, 723.9 ± 190.0 mmoles, $P < 0.01$). No bicarbonate or acetate loss in urine was found during dialysis or the four-hour post-dialysis period.

Our estimates of the percent of acetate metabolized to bicarbonate (M_{Ac}) for each patient in group 1 were 66%, 83%, 91%, 94%, 100%, 102%, 106%, and 106%. For group 2 patients, the estimates were 77%, 78%, 87%, 88%, 88%, 91%, 91%, 101%, 104% and 106%. For all patients the estimated mean percent of acetate converted to bicarbonate in the eight-hour period was 93.5 ± 4.8 (± 1 SEM) for group 1 and 91.1 ± 3.5 for group 2. Thus, our estimates could account for equimolar metabolic conversion of acetate in 50% of group 1 patients and 30% of group 2.

Plasma lipids during hemodialysis. Forty-five percent of the patients studied had fasting hypertriglyceridemia, defined as a plasma triglyceride concentration greater than 140 mg/100 ml. Mean triglyceride values were lower in "new" patients but this difference was not significant ("new": 116.3 ± 58.4, ± 1 SD; "established": 127.3 ± 53.6, $P > 0.1$). No significant sexual bias in triglyceride levels was noted.

Plasma triglycerides fell significantly within 30 min of hemodialysis, reaching the lowest values by mid-dialysis (Fig. 3). The mean decrease for all groups was 52.5 ± 3.0% (± 1 SEM) of the initial triglyceride values with a range of 46 to 60%. There was no significant difference in this decrease among the groups ($P > 0.1$), and the triglyceride decrement varied directly with the administered dose of heparin in all groups ($r = 0.82$). Associated with the decrease in triglycerides was a rise in the plasma total non-esterified free fatty acids (Fig. 3). In group 1 and group 3, mean free fatty acid values were similar ($P > 0.1$). The rise in plasma triglycerides after dialysis was similar in all groups ($P > 0.1$). No significant change in total plasma cholesterol occurred.

Predialysis lipoprotein electrophoretic patterns uniformly revealed beta and pre-beta staining. Chylomicrons were not noted in any patients. Pre-beta stains disappeared early in dialysis and then reappeared during the immediate postdialysis period.

Serum acetoacetate concentration increased during dialysis in all groups (Fig. 4). Peak values were 2.2 mmoles/liter ± 0.4 (± 1 SEM) in group 1, 0.60 ± 0.2 mmoles/liter in group 2, and 0.50 ± 0.2 mmoles/liter in group 3. Group 1 acetoacetate concentrations were significantly greater than groups 2 or 3 concentrations by mid-dialysis ($P < 0.005$). Plasma acetone concentration became detectable at four hours after dialysis in six of eight patients in group 1 and seven of ten in group 2. No significant amounts of acetaldehyde or ethanol were detected.

Discussion

The correction of metabolic acidosis by hemodialysis requires an acetate concentration in the dialysate which is sufficient to increase serum bicarbonate levels, despite significant bicarbonate removal. Mion and his co-workers determined that an acetate concentration of 35 to 40 mmoles/liter fulfilled this requirement for standard surface area dialyzers [1]. However, large surface area hemodialyzers have entered current clinical use in order to provide shorter hours of hemodialysis [21]. These dialyzers transfer acetate very efficiently and, when used with standard commercial concentrates, deliver a large acetate load to the patient. Our purpose was to investigate the acute metabolic effects of this large acetate infusion. The results of the study indicate that the metabolic consequences of high mass-transfer hemodialysis cause significant and complex changes in the acid-base status of the chronic renal failure patient.

Solute mass-transfer. These data demonstrate the efficient nature of solute transfer by the 2.5 m^2 hollow fiber dialyzer. In this study, *in vivo* dialysance data for frequently measured solutes (creatinine, urea, and uric acid) are similar to existing *in vitro* determinations at comparable blood flow rates [22].

Comparison data for glucose transfer for this dialyzer was previously unavailable. Though the use of glucose-free dialysate led to a measurable glucose loss in these patients, it did not introduce a significant energy deficit in patients of groups 1 and 2. The 200 Kcal derived from the metabolism of one mole of infused acetate compensated for the potential caloric loss of 129.6 ± 21.6 Kcal from dialyzed glucose [23]. In fact, the patients of groups 1 and 2 were in positive caloric balance during dialysis.

Acid-base metabolism. The impact of the high mass-transfer dialysis on the acid-base status of hemodialysis patients is depicted schematically in Figure 5. The primary determinants involved are the removal of carbon dioxide and bicarbonate from the patient's blood and the infusion of acetate into the patient.

The magnitude of the carbon dioxide mass-transfer can be appreciated by noting: *1)* the remarkable drop in arterial P_{CO_2} during dialysis (Table 4), *2)* the extremely low P_{CO_2} in the dialyzer venous blood lines, and *3)* that at a Q_B of 300 ml/min, approximately 5%

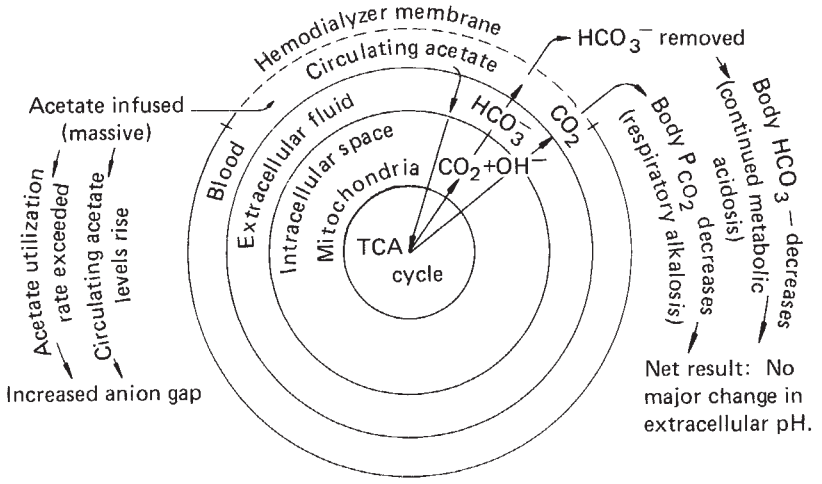

Fig. 5. *Acid-base kinetics during hemodialysis with high mass-transfer hemodialyzers.*

of the cardiac output each minute has almost its entire content of carbon dioxide extracted [24]. During dialysis the arterial P_{CO_2} would reflect the effects of both alveolar ventilation and dialyzer diffusion. The depressed arterial P_{CO_2} values observed in our patients during dialysis are adequately explained by carbon dioxide mass-transfer. Pulmonary hyperventilation could theoretically explain the decreased arterial P_{CO_2} [5]; however, no increase in minute ventilation occurred, and a trend toward alveolar hypoventilation was observed in early dialysis. Therefore, alveolar hyperventilation as the explanation of respiratory alkalosis during dialysis is inconsistent with our observations. Others have observed similar venous dialyzer line P_{CO_2} values [4] and minute ventilation volumes during dialysis [25]. It is apparent that carbon dioxide dialysance accounts for the early rise in arterial pH which occurred in these patients.

In both groups 1 and 2, the mean rate of bicarbonate removal exceeded the estimated mean intradialytic rate of bicarbonate generation. As a result, the serum levels of bicarbonate decreased during dialysis, despite ongoing bicarbonate generation. These results contrast to previous observations of steadily rising intradialytic bicarbonate concentration [25, 26]. These latter studies were done using standard surface area dialyzers and lower blood flow rates. We emphasize that in our patients the depressed serum bicarbonate levels do not reflect a diminished ability to convert acetate, but merely indicate a rapid bicarbonate removal which exceeds the normal rate that one can expect bicarbonate to be generated. These observations disagree with previous studies interpreting similar results as "acetate intolerance" in hemodialysis patients [5].

At the conclusion of hemodialysis, the preexisting metabolic acidosis has been worsened (Fig. 5). In clinically stable outpatients with chronic renal failure and mild bicarbonate deficit, the acute bicarbonate decrease is balanced by carbon dioxide removal by the dialyzer, resulting in an actual increase in arterial pH. However, in acutely ill patients with more severe bicarbonate deficit and diminished buffer reserve, the rapid bicarbonate removal could have serious consequences. Therefore, the use of a large surface area dialyzer and acetate-containing dialysate could lead to deterioration of acid-base balance.

The dialysis delivery system utilized had a profound effect upon bicarbonate removal by the hemodialyzer. In the recirculating single pass system (group 2), the equilibration of measurable amounts of bicarbonate in the recirculating dialysate helped attenuate bicarbonate removal and mitigated the drop in arterial bicarbonate concentrations that was observed with the single pass system. Since this effect also applies to other solutes (urea, creatinine), the clearance of these solutes was also diminished in the recirculating pass system. While others have noted a delivery system influence on dialyzer clearance [21], the importance of this aspect to bicarbonate kinetics has not been emphasized previously.

In contrast to previous reports of elevated lactate and pyruvate levels [4, 26], we were unable to demonstrate any significant change in these parameters. In this study, the intradialytic increase in unmeasured circulating anions could be accounted for by the increase in the circulating acetate anion (Table 6).

As will be discussed, hemodialysis under our study conditions appears to favor ketogenesis. During conditions favoring ketogenesis, serum pyruvate levels have been reported to decrease [7, 27] or remain stable, which is consistent with our results.

When the alkalinizing salt is acetate, the interval that follows dialysis is characterized by continued bicarbonate generation and rapid increase in serum bicarbonate concentrations. During this interval circulating acetate disappears within two hours, but maximum arterial bicarbonate levels are not reached until four hours after dialysis. This delayed bicarbonate rise probably represents transport and metabolism of the remaining intracellular acetate. Others have implied delayed acetate metabolism in patients who continue to elevate their serum bicarbonate up to 12 hr after dialysis [26]. We could not confirm the latter observation. Postdialysis metabolic alkalosis [3, 25, 26, 28] and its attendant complications to the hemodialysis patient [29, 30, 31] have been described earlier. It is apparent that bicarbonate buffered dialysate produces a more physiologic correction of metabolic acidosis [32, 33].

Acetate metabolism. The use of large surface area dialyzers and high dialysate acetate concentrations (40 mmoles/liter) results in acetate infusion of a magnitude which exceeds the metabolic capacities of dialysis patients. This leads to a progressive increase in plasma acetate concentrations during dialysis (Fig. 1).

When acetate was infused at the apparent maximum rate of utilization of exogenous acetate (group 2), a steady state was reached and serum concentrations did not vary. Kveim and Nesbakken used an analogous approach to obtain comparable data [3]. Group 1 studies indicate that increasing the rate of acetate infusion does not further increase the intradialytic rate of bicarbonate generation. At the conclusion of dialysis, the percent decrement in acetate is constant until the acetate concentration no longer saturates the metabolic systems (Fig. 2). In group 2, the disappearance curve splays below 3.0 mmoles/liter. This may represent the concentration at which the metabolic rate of acetate varies with its concentration. It would be expected, then, that after initiation of dialysis, when the serum concentration exceeds 3.0 mmoles/liter, a constant rate of acetate utilization may occur. This can be seen in Figure 1. While availability of coenzyme A may be important, the rate-limiting factor in acetate metabolism is unknown at present.

Acetate entry into the tricarboxylic acid cycle. Earlier data had indicated that equimolar generation of bicarbonate from acetate uniformly occurs during dialysis [1]. The latter investigation was performed on a few patients with smaller surface area hemodialyzers operating at lower blood flow rates. Our results suggest that estimated acetate entry into the tricarboxylic acid cycle may be more variable. We found that equimolar oxidative generation of sodium bicarbonate from sodium acetate does not occur in the majority of patients. This disparity could result from the experimental conditions of our investigations.

Our estimation of acetate entry into the tricarboxylic acid cycle is an indirect method which is based upon assumed alterations in total body bicarbonate attendant to hemodialysis (Appendix, equations 7a to f, 8). The basic assumption of our method depends upon the total body water and the bicarbonate space remaining constant. Water loss during hemodialysis in our patients resulted in a contraction of the total body water compartment of less than 1.5% during these studies. Based upon changes in the estimated total body bicarbonate, four out of eight patients in group 1 and seven out of ten patients in group 2 did not appear to have equimolar conversion of acetate to bicarbonate. If these estimates are correct, this would provide a significant amount of acetate that would theoretically be available to enter alternate metabolic pathways.

Lipsky et al have reviewed the subject of ketone production in man [7]. They have noted that sodium acetate infusion into individuals leads to a rise in serum ketones. This rise was attributed either to alkalosis or acetate condensation. Additional explanations are possible in our patients. Fasting, as well as heparin-induced lipolysis can lead to elevated plasma free fatty acid concentrations and subsequent ketone production. However, the latter factors were operative in groups 3 patients, and although they were the only group in negative caloric balance, they had the least amount of ketone formation. Patients in group 1 received the largest acetate infusions, and they raised their plasma acetoacetate levels significantly higher than did patients in group 2. The blood pH change for both groups was similar and did not rise during the intradialytic period. Acetate condensation, therefore, would appear to be the primary ketogenic mechanism in these subjects.

Plasma lipids during hemodialysis. Fasting hypertriglyceridemia has been widely observed in uremic patients [34, 35]. Our data are consistent with these observations. We attribute the decrease of triglycerides during hemodialysis to the effect of heparin on lipoprotein lipase activity for the following reasons: *1)* there was a direct statistical correlation of the triglyceride decrease and the amount of heparin infused, *2)* the disappearance of pre-beta staining from the lipoprotein electrophoresis occurred at the same time, and *3)* the simultaneous reappearance of pre-beta staining with rising triglyceride levels after dialysis. The rise in plasma free fatty acids during

dialysis further documents the triglyceride lipolysis. A similar rise has been reported by others [36]. Triglyceride resynthesis proceeds in the active metabolic interval immediately after dialysis.

In this study, the effect of a solitary dialysis and its related acetate infusion does not appear to be different from bicarbonate buffered dialysis in its effects on the level of plasma triglycerides. However, we recognize that this does not clarify whether recurrent infusion of large amounts of acetate would ultimately influence triglyceride values.

We conclude that solute transfer during hemodialysis with large surface area dialyzers has significant impact on the acid-base and metabolic status of the patient as follows: *1)* carbon dioxide dialysance results in an early pH increase during dialysis, *2)* bicarbonate removal appears to exceed bicarbonate generation as evidenced by the fall in serum bicarbonate during dialysis, *3)* under conditions of the study, the infusion of acetate exceeds the maximum utilization rate of exogenous acetate and results in increased plasma acetate levels during dialysis, *4)* with massive acetate infusion, bicarbonate generation after dialysis results in the development of significant alkalosis, *5)* under these experimental conditions acetate may enter alternate pathways of metabolism and may not entirely be accounted for by bicarbonate generation, *6)* it appears that an acetate concentration of 40 mmoles/liter in the dialysate may have significant adverse metabolic effects when used with a 2.5 m^2 hollow fiber dialyzer and single pass delivery system, and *7)* the rise in non-esterified free fatty acids and decrease in plasma triglycerides can be directly attributed to the heparin administered during dialysis.

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Reprint requests to Dr. Edmund J. Lewis, Rush-Presbyterian-St. Luke's Medical Center, 1753 West Congress Parkway, Chicago, Illinois 60612, U.S.A.

Appendix

Calculations for acetate and bicarbonate kinetics of hemodialysis

Clearance (C):

$$C(\text{liters/min}) = \frac{Q_{B_i}C_{B_i} - (Q_{B_i} - Q_F)C_{B_0}}{C_{B_i}} \qquad 1a$$

where C_{B_i} is the solute concentration at the dialyzer blood inlet (mmoles/liter), C_{B_0} is the solute concentration at the dialyzer blood outlet, Q_{B_i} is the blood flow rate into the dialyzer (liters/min), and Q_F is the ultrafiltration rate (liters/min).

Dialysance (D):

$$D(\text{liters/min}) = \frac{Q_{B_i}C_{B_i} - (Q_{B_i} - Q_F)C_{B_0}}{C_{B_i} - C_{D_i}} \qquad 1b$$

where C_{D_i} is the solute concentration at the dialysate inlet (mmoles/liter).

Mass transfer rate (N) *for acetate* (Ac) *(acetate infusion rate):*

$$N_{Ac}\ (\text{mmoles/min}) = (Q_{B_i} - Q_F)C_{B_{0_{Ac}}} - Q_{B_i}C_{B_{i_{Ac}}} \qquad 2a$$

Blood concentration of acetate at dialyzer inlet ($C_{B_{i_{Ac}}}$):

$$C_{B_{i_{Ac}}}\ (\text{mmoles/liter}) = C_{P_{i_{Ac}}}[(1 - f_{RBC}) + 0.59(f_{RBC})] \qquad 2b$$

where $C_{P_{i_{Ac}}}$ is the plasma concentration of acetate at the dialyzer blood inlet (mmoles/liter), f_{RBC} is the fraction of blood volume occupied by the red blood cells (hematocrit), and 0.59 is the fractional amount of acetate in RBC's relative to plasma in the blood entering the dialyzer.

Blood concentration of acetate at the dialyzer outlet ($C_{B_{0_{Ac}}}$):

$$C_{B_{0_{Ac}}}\ (\text{mmoles/liter}) = C_{P_{0_{Ac}}}[(1 - f_{RBC}) + 0.49\ (f_{RBC})] \qquad 2c$$

where $C_{P_{0_{Ac}}}$ is the plasma acetate concentration at the dialyzer blood outlet.

Acetate kinetics calculated from N_{Ac}:

Acetate infused (Inf. Ac) each $\text{hour}_{(1,2,3,4)}$ (mmoles):

$$\text{Inf. Ac}_{(1,2,3,4)} = N_{Ac} \cdot 60\ , \qquad 3a$$

where N_{Ac} is calculated from the mean concentrations of acetate for each hourly period of dialysis.

Total acetate infused (T. Inf. Ac):

$$\text{T. Inf. Ac (mmoles)} = \text{Inf. Ac}_1 + \text{Inf. Ac}_2 + \text{Inf. Ac}_3 + \text{Inf. Ac}_4 \qquad 3b$$

Mean acetate infusion rate ($\bar{N}_{Ac}$):

$\bar{N}_{Ac}$ (μmoles/min/kg)

$$= \frac{\text{T. inf. Ac}}{W} \times \frac{1}{240} \times 1000 \qquad 4$$

where W is the body wt in kg.

Maximum rate of utilization of exogenous acetate (R_{Ac}):

R_{Ac} (μmoles/min/kg)

$$= \frac{Inf.\ Ac_{(1,2,3,4)}}{W} \times \frac{1}{60} \times 1000 \qquad 5$$

Acetate disappearance rate (k_{Ac}):

$$k_{Ac}\ (\mu\text{moles/liter/min}) = \frac{Ac_0 - Ac_{x\ min}}{X\ min} \qquad 6$$

where Ac_0 is the plasma arterial concentration at four hours (completion) of dialysis (μmoles/liter), $Ac_{x\,min}$ is the arterial concentration x minutes after the termination of dialysis.

Amount of bicarbonate (HCO_3) *generation:*

Total body HCO_3 predialysis ($TBHCO_{3_{pre}}$):

$$TBHCO_{3_{pre}}\ (\text{mmoles}) = 0.6 \times W \times HCO_{3_{pre}}, \qquad 7a$$

where 0.6 is the estimated space of bicarbonate distribution as 60% of total body wt, and $HCO_{3_{pre}}$ is the predialysis serum bicarbonate concentration in mmoles/liter.

Amount of bicarbonate removed (HCO_{3_r}) *hourly (mmoles):*

$$HCO_{3_{r(1,2,\ldots x)}} = 60\ [Q_{BI}C_{Bi_{\overline{HCO_3}}} - (Q_{B_i} - Q_F)C_{B_{o_{\overline{HCO_3}}}} \qquad 7b$$

where $C_{Bi_{\overline{HCO3}}}$ is the mean bicarbonate concentration in the arterial dialyzer line for any given hour, and $C_{B_{o_{\overline{HCO3}}}}$ is the mean bicarbonate concentration in the venous dialyzer line for the same period.

Total bicarbonate removed (T. HCO_{3_r}):

$$\text{T. } HCO_{3_r}(\text{mmoles}) = HCO_3r_1 + HCO_3r_2 + HCO_3r_3 + HCO_3r_4 \qquad 7c$$

Nonextracted body bicarbonate (HCO_{3n}):

$$HCO_{3_n}\ (\text{mmoles}) = TBHCO_{3_{pre}} - \text{T. } HCO_{3_r} \qquad 7d$$

Total body bicarbonate at 4 hr after dialysis ($TBHCO_{3_{post}}$):

$$TBHCO_{3_{post}}\ (\text{mmoles}) = 0.6 \times W \times HCO_{3_{post}}, \qquad 7e$$

where $HCO_{3_{post}}$ is the highest serum bicarbonate concentration (4 hr) after dialysis.

Amount of bicarbonate generation (T.HCO_{3G}):

$$\text{T. } HCO_{3_G}\ (\text{mmoles}) = TBHCO_{3_{post}} - HCO_{3_n} \qquad 7f$$

Estimated percent of infused acetate metabolized to bicarbonate (M_{Ac}):

$$M_{Ac} = \frac{\text{T.}HCO_{3_r}}{\text{T. Inf. Ac}} \times 100 \qquad 8$$

Mean intradialytic bicarbonate generation rate ($\bar{R}_{HCO_3}$):

Total body bicarbonate at 4th hr of dialysis ($TBHCO_{3_4}$):

$$TBHCO_{3_4}\ (\text{mmoles}) = 0.6 \times W \times HCO_{3_4} \qquad 9a$$

where HCO_{3_4} is the serum bicarbonate concentration at the 4th hour of dialysis. The following equation applies for $TBHCO_{3_4}$:

$$TBHCO_{3_4}\ (\text{mmoles}) = TBHCO_{3_{pre}} + HCO_{3_g} - \text{T.}HCO_{3_r}$$

where HCO_{3_g} is the amount of bicarbonate generated during the dialysis. The above equation can be rewritten to solve for HCO_{3_g}:

$$HCO_{3_g}\ (\text{mmoles}) = TBHCO_{3_4} + \text{T.}HCO_{3_{rr}} - TBHCO_{3_{pre}} \qquad 9b$$

Mean rate of bicarbonate generation during dialysis ($\bar{R}_{HCO_3}$):

$\bar{R}_{HCO_3}$ (μmoles/min/kg)

$$= \frac{HCO_{3_g}}{W} \times \frac{1}{240} \times 1000 \qquad 9c$$

Mean rate of bicarbonate removal during dialysis ($\bar{N}_{HCO_3}$):

$\bar{N}_{HCO_3}$ (μmoles/min/kg)

$$= \frac{\text{T.}HCO_{3_r}}{W} \times \frac{1}{240} \times 1000 \qquad 10$$

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